US005990110A

United States Patent [19]

Firestone

[11] **Patent Number: 5,990,110**

[45] **Date of Patent: Nov. 23, 1999**

[54] **METHOD FOR TREATING TUMORS HAVING HIGH LDL REQUIREMENTS EMPLOYING MTP INHIBITORS**

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[21] Appl. No.: **08/914,062**

[22] Filed: **Jul. 15, 1997**

[51] **Int. Cl.**[6] **A61K 31/495**; A61K 31/445

[52] **U.S. Cl.** **514/252**; 514/326; 514/329

[58] **Field of Search** 514/252, 326, 514/329

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,712,279 1/1998 Biller et al. 514/252

OTHER PUBLICATIONS

Firestone, R.A. "Low–Density Lipoprotein as a Vehicle for Targeting Antitumor Compounds to Cancer Cells" Bioconjugate Chem., vol. 5, No. 2, 1994, pp. 105–113.

Wunderlich, M. et al, "The Redox Properties of Protein Disulfide Isomerase (DsbA) of *Escherichia coli* Result from a Tense Conformation of its Oxidized Form", J. Mol. Biol. (1993) 233, 559–566.

Firestone, R.A. et al, "Selective Delivery of Cytotoxic Compounds to Cells by the LDL Pathway" Journal of Medicinal Chem., 1984, vol. 27, No. 8, pp. 1037–1043.

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Attorney, Agent, or Firm—Burton Rodney

[57] **ABSTRACT**

A method is provided for treating hematologic tumors and solid tumors, including certain types of leukemias and metastatic tumors, having high LDL requirements employing a delipidating agent such as an MTP inhibitor to substantially reduce LDL blood levels. In addition, a method is provided for treating tumors of the above types having high LDL requirements, especially hematologic tumors such as certain leukemias, employing a delipidating compound to substantially remove native LDL, and then administering a cytotoxic agent carried in reconstituted LDL.

29 Claims, No Drawings

METHOD FOR TREATING TUMORS HAVING HIGH LDL REQUIREMENTS EMPLOYING MTP INHIBITORS

FIELD OF THE INVENTION

The present invention relates to a method for treating cancers having high LDL requirements employing a delipidating agent, which preferably is an MTP inhibitor, alone or in combination with a cytotoxic agent.

BACKGROUND OF THE INVENTION

It is known that cancer cells need cholesterol to make new cell membrane. The cholesterol is supplied by either de novo synthesis or from low-density lipoprotein (LDL), or both, Firestone, R. A. et al, "Selective Delivery of Cytotoxic Compounds to Cells by the LDL Pathway, J. Med. Chem., 1984, 27, 1037–1043. Firestone et al describe a series of cytotoxic compounds that are compatible with reconstituted LDL and may be delivered with reconstituted LDL against cancers that copiously internalize LDL.

Firestone, R. A., "Low-Density Lipoprotein as a Vehicle for Targeting Antitumor Compounds to Cancer Cells", Bioconjugate Chemistry, 1994, 5, pp 105–113, at page 105, in the "Introduction", discusses problems associated with cancer treatment as follows:

"It is difficult to eradicate cancer cells in vivo because they share with normal cells, for the most part, the same biochemical machinery. There is no cytotoxic substance that is completely selective for malignant cells, and all those presently in use cause dose-limiting toxic side effects. For this reason there is a growing emphasis on targeting, i.e., selective delivery of drugs to tumors in ways that bypass normal body tissues.

"Among the vehicles that can be used for this purpose is low-density lipoprotein (LDL), a normal blood constituent that is the body's principal means for delivery of cholesterol to tissues. Cholesterol, a major constituent of mammalian cell membranes, is obtained by cells either by making it themselves or by picking it up from LDL or both. Cancer cells, like all dividing ones, need large amounts of cholesterol because they are making new membrane. There is ample evidence that many types of cancer cells indeed have unusually great LDL requirements. The evidence is 2-fold: measurements of LDL uptake by tumor cells and depletion of LDL in the blood of cancer patients resulting from high uptake by the tumor (viae infra). Thus, if LDL could be made to carry antitumor drugs, it would serve as a targeting vehicle. This concept was proposed in 1981–2 (1,2) and has been reviewed several times since then (3–7)."

(1) Gal, D., Ohashi, J., MacDonald, P. C., Buchsbaum, H. J., and Simpson, E. R. (1981) Low-density lipoprotein as a potential vehicle for chemotherapeutic agents and radionucleotides in the management of gynecologic neoplasms. *Am. J. Obstet. Gynecol.* 139, 877.

(2) Counsell, R. E., and Pohland, R. C. (1982) Lipoproteins as potential site-specific delivery systems for diagnostic and therapeutic agents. *J. Med. Chem.* 25, 1115.

(3) van Berkel, T. J. C. (1993) Drug targeting: application of endogenous carriers for site-specific delivery of drugs. *J. Controlled Release* 24, 145.

(4) Vitols, S. (1991) Uptake of low-density lipoprotein by malignant cell—possible therapeutic applications. *Cancer Cells* 3, 488.

(5) deSmidt, P. C., and Van Berkel, T. J. C. (1990) LDL-mediated drug targeting. *Crit. Revs. Thera. Drug Carrier Syst.* 7, 99.

(6) Peterson, C., Masquelier, M., Rudling, M., S öderberg, K., and Vitols, S. (1991) Lipoproteins, malignancy and anticancer agents. *Targeted Diagn. Ther. (U.S.)* 5, 175.

(7) Catapano, A. L. (1987) Transport of cytotoxic compounds to cells via the LDL receptor pathway. *Med. Sci. Res.* 15, 411.

At page 105 under the topic "LDL Uptake . . .", Firestone, supra, lists numerous tumor types that have especially high LDL requirements including acute myeloid leukemia (AML), human monocytic (FAB-M5) and myelomonocytic (FAB-M4) leukemias, chronic myeloid leukemia in blast crisis, solid tumors such as epidermoid cervical cancer EC-50, endometrial adenocarcinoma AC-258, gastric carcinoma and parotid adenoma, G2 heptoma, squamous lung cancer, choriocarcinoma, brain tumors such as medulloblastoma, oligodendroglioma, glioma V-251MG, and malignant menigioma, as well as tumor cells that are exceptionally metastatic

(Schroeder, F., Kier, A. B. Olson, C. D., and Dempsey, N. E. (1984) Correlation of tumor metastasis with sterol carrier protein and plasma membrane sterol levels. *Biochem. Biophys. Res. Commun.* 124, 283, and

Cambien, F., Ducimetiere, P., and Richard, J. (1980) Total serum cholesterol and cancer mortality in a middle-aged male population. *Am. J. Epidemiol.* 112, 388),

tumor cells that are exceptionally aggressive

(Rudling, M. J., Stahle, L., Peterson, C. O., and Skoog, L. (1986) Content of low density lipoprotein receptors in breast cancer tissue related to survival of patients. *Brit. Med. J.* 292, 580;

Peterson, C., Vitols, S., Rudling, M., Blomgren, H., Edsmyr, F., and Skoog, L. (1985) Hypocholesterolemia in cancer patinets may be caused by elevated LDL receptor activities in malignant cells. *Med. Oncol. Tumor Pharmacother.* 2, 143;

Muller, C. P., Wagner, A. U., Maucher, C., and Steinke, B. (1989) Hypocholesterolemia, an unfavorable feature of prognostic value in chronic myeloid leukemia. *Eur. J. Hematol.* 43, 235),

and tumor cells that are exceptionally undifferentiated

(Ponec, M., Havekes, L., Kempenaar, J., Lavrijsen, S., Wijsman, M., Boonstra, J., and Vermeer, B. J. (1985) Calcium-mediated regulation of the low density lipoprotein receptor and intracellular cholesterol synthesis in human epidermal keratinocytes. *J. Cell Physiol.* 125 98;

Zyada, L. E., Hassan, H. T., Rees, J. K. H., and Ragab, M. H. (1990) The relation between hypocholesterolemia and degree of maturation in acute myeloid leukemia. *Hematol. Oncol.* 8, 65;

Ponec, M., Havekes, L., Kempenaar, J., Lavrisen, S., and Vermeer, B. J. (1984) Defective low-density lipoprotein metabolism in cultured, normal transformed and malignant keratinocytes. *J. Invest. Dermatol.* 83, 436).

Firestone, supra, on page 107 under the topic "Reconstitution of LDL With Cytotoxic Drugs" states as follows,

"In order to kill tumors with drugs that are targeted in LDL, the drugs must somehow be bound to the LDL in such a way that (1) they cannot escape from it while traveling in the blood enroute to the tumor, (2) their cytotoxicity is chemically or physically masked while LDL-bound, and then restored after entering the target

cells, (3) in quantity X killing power there is enough drug to kill cancer cells contained in the reconstituted LDL (r-LDL), whose uptake is limited by the number of LDL receptors on the tumor cells and their rate of internalization, and (4) the presence of Apo B and its binding power to LDL receptors are retained. The ability of the drug, once released from its carrier, to escape from lysosomes must also be taken in account (76)."

((76) Burton, R., et al (1975) The permeability properties of rat liver lysosomes to nucleotides. *Biochem. Soc. Trans.* 3, 1251).

On page 109, under the topic "Removal of LDL From the Patient Before Treatment", Firestone, supra, states as follows,

"During treatment, drug-bearing r-LDL must compete with native LDL for access to LDL receptors on the tumor cells, requiring elevated doses of r-LDL. This can be countered by removing LDL from the patients' blood (delipidation) prior to treatment (139–141). Although restoration of normal LDL levels takes days (141), it might be best to delipidate immediately prior to treatment because it induces upregulation of LDL receptors throughout the body (142), and it is unknown whether upregulation in this way would be greater for tumor or normal cells."

((139) Franceschini, G., Busnach, G., Calabresi, L., Chiesa, G., Gianfranceschi, G., Zoppi, F., Minetti, L., and Sirtori, C. R. (1991) Predictability of low-density lipoprotein levels during apheretic treatment of hypercholesterolemia. *Eur. J. Clin. Invest.* 21, 209.

(140) Saal, S. D., Parker, T. S., Gordon, B. R., Studebaker, J., Hudgins, L., Ahrens, E. H., Jr., and Rubin, A. L. (1986) Removal of low-density lipoproteins in patients by extracorporeal immunoadsorption. *Am. J. Med.* 80, 583.

(141) Parker, T. S., Gordon, B. R., Saal, S. D., Rubin, A. L., and Ahrens, E. H., Jr. (1986) Plasma high density lipoprotein is increased in man when low density lipoprotein (LDL) is lowered by LDL-pheresis. *Proc. Nat. Acad. Sci. U.S.A.* 83, 777.

(142) Goldstein, J. L., and Brown M. S. (1977) The low-density lipoprotein pathway and its relation to atherosclerosis. *Annu. Rev. Biochem.* 46, 897).

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, *Chem. Phvs. Lipids* 38, 205–22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The protein from bovine liver has been isolated and characterized. Wetterau & Zilversmit, *Chem. Phys. Lipids* 38, 205–22 (1985). Polyacrylamide gel electrophoresis (PAGE) analysis of the purified protein suggests that the transfer protein is a complex of two subunits of apparent molecular weights 58,000 and 88,000, since a single band was present when purified MTP was electrophoresed under nondenaturing condition, while two bands of apparent molecular weights 58,000 and 88,000 were identified when electrophoresis was performed in the presence of sodium dodecyl sulfate (SDS). These two polypeptides are hereinafter referred to as 58 kDa and 88 kDa, respectively, or the 58 kDa and the 88 kDa component of MTP, respectively, or the low molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau et al., *J. Biol. Chem.* 265, 9800–7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa–88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine TP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, *Nature* 335, 649–51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu et al., *J. Biol. Chem.* 262, 6447–9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer activity. Wetterau et al., *Biochemistry* 30, 9728–35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, *Biochem. Biophys. Acta* 875, 610–7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in *The Metabolic Basis of Inherited Disease*, Sixth edition, 1139–64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20–45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., *Clin. Chem.* 34, B9–12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., *J. Clin. Invest.* 82, 1803–6 (1988) and Huang et al., *Am. J. Hum. Genet.* 46, 1141–8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel, supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy,

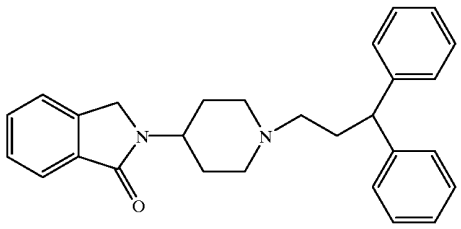
degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, *Biochem. Biophys. Acta* 875, 610–7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

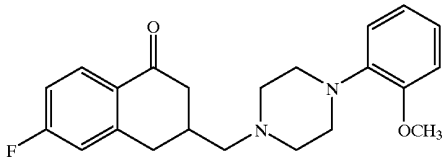
Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., *J. Biol. Chem.* 263, 4434–42 (1988). Their results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled. MTP may play a role in this process. In support of this hypothesis, Howell and Palade, *J. Cell Biol.* 92, 833–45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. iggins and Hutson, *J. Lipid Res.* 25, 1295–1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event. However, there is no direct evidence in the prior art demonstrating that MTP plays a role in lipid metabolism or the assembly of plasma lipoprotein.

Recent reports (Science, Vol. 258, page 999, 1992; D. Sharp et al, Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

Canadian Patent Application No. 2,091,102 published Mar. 2, 1994 (corresponding to U.S. application Ser. No. 117,362, filed Sep. 3, 1993 (file DC21b)) which is incorporated herein by reference), reports MTP inhibitors which also block the ipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



which has the name 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-3-oxo-1H-isoindole hydrochloride and



which has the name 1-[3-(6-fluoro-1-tetralanyl)methyl]-4-O-methoxyphenyl piperazine.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, a method is provided for treating tumors having high LDL requirements which method includes the step of administering to a mammalian species in need of treatment a therapeutically effective amount of a delipidating agent to substantially reduce LDL blood levels.

In the above method, the delipidating agent may be optionally administered in combination with a cytotoxic agent.

In addition, in accordance with the present invention, a method is provided for treating tumors having high LDL requirements, especially hematologic tumors, which method includes the steps of administering to a mammalian species in need of treatment a therapeutically effective amount of a delipidating agent to substantially remove LDL (that is, native LDL), and administering a cytotoxic agent carried in reconstituted LDL (rLDL-drug conjugate).

The delipidating compound to be employed in the methods of the invention may be an LDL lowering compound which lowers LDL down to less than 20% of normal (that is less than 20% of 150 mg/dl that is 30 mg/dl), preferably down to less than 10% of normal (that is less than 15 mg/dl) and most preferably to substantially zero LDL. Examples of delipidating agents which may be employed herein include MTP inhibitors, statins, fibrates and resins or combinations thereof, with MTP inhibitors being preferred.

The reconstituted LDL (employed as a carrier for the cytotoxic agent in the above method) may be prepared according to the procedures described in the review article Firestone, R. A., Low-Density Lipoprotein as a Vehicle for Targeting Antitumor Compounds to Cancer Cells, Bioconjugate Chemistry, 1994, 5, 105–113, such as disclosed in the following references cited by Firestone, supra:

(78) Krieger, M., Brown, M. S., Faust, J. R., and Goldstein, J. L. (1978) Replacement of endogenous cholesteryl esters of low density lipoprotein with exogenous cholesteryl linoleate, *J. Biol. Chem.* 253, 4093.

(79) Krieger, M., McPhaul, J. J., Goldstein, J. L., and Brown, M. S. (1979) Replacement of neutral lipids of low density lipoprotein with esters of long chain unsaturated fatty acids, *J. Biol. Chem*. 254, 3845.

(104) Lundberg, B. (1987) Preparation of drug-low density lipoprotein complexes for delivery of antitumoral drugs via the low density lipoprotein pathway, *Cancer Res*. 47, 4105, and

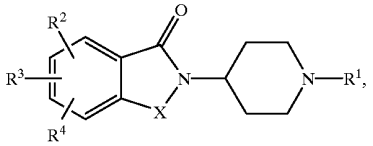
Gene M. Dubowchik and Raymond A. Firestone, *Tet. Lett*. 35, 4523, 1994.

The cytotoxic agent may be incorporated in the reconstituted LDL to form an LDL-drug conjugate following the procedure described in the Firestone review article, supra, especially as described in cited reference (104) Lundberg, supra.

MTP inhibitors to be employed in the methods of the invention include MTP inhibitors disclosed in Canadian Patent Application No. 2,091,102 described hereinbefore (corresponding to U.S. application Ser. No. 117,362), U.S. application Ser. No. 472,067, filed Jun. 6, 1995 (file DC21e), U.S. application Ser. No. 548,811 (file DC21h), U.S. provisional application No. 60/017,224, (file HX79a*), U.S. provisional application No. 60/017,253, (file HX82*) and U.S. provisional application No. 60/017,254, (file HX84*).

All of the above U.S. applications are incorporated herein by reference.

The MTP inhibitors disclosed in U.S. application Ser. No. 472,067, filed Jun. 6, 1995 (file DC21e) are piperidine compounds of the structure



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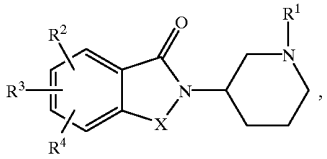

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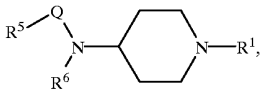

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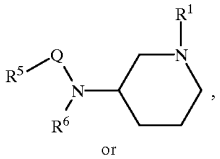

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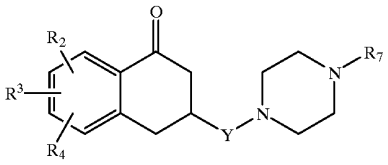
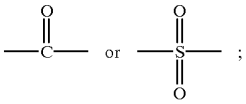
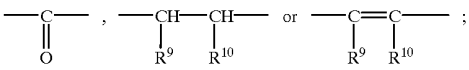


where Q is



X is: CHR^8,



R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is $—(CH_2)_m—$or

wherein m is 2 or 3;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cyclo-alkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or R^1 is a fluorenyl-type group of the structure

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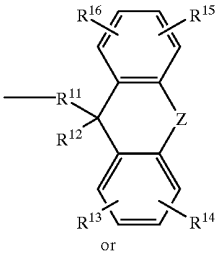

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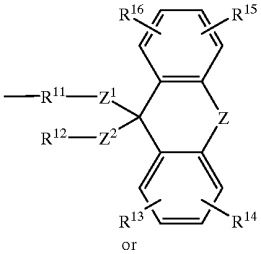

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